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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CLARK, SARA E	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,918	BIEBERSCHULTE ET AL.	
	Examiner	Art Unit	
	SARA E. CLARK	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *09 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *15-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/31/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

This application is a 35 U.S.C. 371 (national stage) application of PCT/CH03/00523, filed 7/30/2003, which claims benefit of priority to Swiss application number 1357/02, filed 7/31/2002. Claims 1-38, as amended, are pending.

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-14) in the reply filed on 4/9/2009 is acknowledged.

2. Claims 15-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/9/2009.

Priority

3. Acknowledgment is made of applicant's claim to foreign priority under 35 U.S.C. 119(a)-(d). Claims 1-38 are entitled to an effective filing date of 7/30/2003.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 1/31/2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 112

Indefiniteness

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-14 recite the limitations "especially for" and "if necessary," and claims 10 and 12 recite the limitation "preferably," which are by nature open-ended, rendering the claims indefinite because it is unclear whether the limitations following the phrases are part of the claimed invention. See MPEP § 2173.05(d).

Further, while the term "trans-tympanic" is reasonably understood to indicate a formulation for administration across the tymapnic membrane, the term "intra-transtympanic" is indefinite, since how a formulation might be applied both across ("trans") and within or inside ("intra") the tympanic membrane is not immediately apparent, and the specification does not elaborate.

In order to overcome this ground of rejection the examiner recommends omitting the words "especially," "if necessary," and "preferably," and amending the preamble of claim 1 (for example, "a pharmaceutical formulation for trans-tympanic or intra-tympanic administration" or "a trans-tympanic or intra-tympanic pharmaceutical formulation").

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ehrenberger et al. (US Pat. 5,563,140, issued 10/8/1996) in view of Petrus (US Pat. 6,093,417, issued 7/25/2000).

Ehrenberger et al. teach a small genus of quinoxalin-2-one compounds including caroverine (1-diethylaminoethyl-3-(p-methoxybenzyl)-1,2-dihydro-quinoxalin-2-one), where the general formula substituents R1 and R2 are ethyl, n is 2, and R3 is methoxy (col. 1, lines 10-30), as recited in claims 1 and 2. Also taught is the same compound in which R3 is hydroxy, yielding the compound 1-diethylaminoethyl-3-(p-hydroxybenzyl)-1,2-dihydro-quinoxalin-2-one, as recited in claims 1 and 3. Ehrenberger et al. disclose these compounds in liquid formulations for application to cochlea in the treatment of functional disturbances of the inner ear such as tinnitus (col. 6, lines 6-22). Also taught are pharmaceutical dosage forms including these compounds with carriers, excipients, lubricants, and bulking agents (col. 5, lines 58-63).

However, Ehrenberger et al. do not teach the formulation of these compounds with a permeability accelerator (a.k.a. permeation or penetration enhancer).

Petrus teaches topical ear compositions using DMSO, propylene glycol and admixtures thereof as penetration enhancers for more effective drug absorption though the tympanic membrane (abstract; col. 4, lines 1-15), citing the risks of surgical treatment such as tympanostomy, which can require general anesthesia (col. 2, lines 31-60). Local application of therapeutic agents to the inner ear also places a high dose in direct proximity to the targeted receptors and avoids disadvantages of oral

administration, which disperses the drug systemically and may result in undesirable side effects. One of ordinary skill in the art, then, would have been motivated to apply caroverine derivatives directly to the inner ear, using penetration enhancers to promote tympanic uptake and absorption.

Neither Ehrenberger nor Petrus disclose (a) DMSO as 5% to 50% (w/w) of the formulation as recited in claim 6; (b) a ratio of active compound to permeability accelerator, as recited in claim 10; or (c) a quantified viscosity level for a particular formulation, as recited in claim 12. However, the recited weight percent range (5% to 50%) and weight ratios (1:2 to 1:500) cover a very broad range, as does the recited viscosity, in the range of 5000 to 25000 mPA·s. The narrowing "preferably" clauses recite merely optional limitations, and the disclosure supplies no particular reason, let alone evidence of criticality, for the percentage weight range of claim 6, the ratio range of claim 10, or the viscosity range of claim 12. As recognized by MPEP § 2144.05,

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods and caroverine compounds as taught by Ehrenberger et al. with the solvents and permeation enhancers as taught by Petrus, because one of ordinary skill would have had a reasonable expectation of success in treating inner ear conditions by directly administering agents known in the treatment of tinnitus to the tympanic membrane,

which would avoid the risks of conventional treatments while achieving a simpler, more direct route of administration with greater patient comfort.

9. Claims 11, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ehrenberger et al. (US Pat. 5,563,140, issued 10/8/1996) in view of Petrus (US Pat. 6,093,417, issued 7/25/2000) as applied to claims 1-10 and 12 above, and further in view of Mantelle (US Pat. 5,446,070, issued 8/29/1995).

As discussed above, Ehrenberger et al. teach the compounds caroverine (1-diethylaminoethyl-3-(p-methoxybenzyl)-1,2-dihydro-quinoxalin-2-one), and "hydroxy-caroverine" (1-diethylaminoethyl-3-(p-hydroxybenzyl)-1,2-dihydro-quinoxalin-2-one), in liquid formulations for application to cochlea, as well as in pharmaceutical dosage forms with carriers and excipients. Petrus teaches topical ear compositions using DMSO, propylene glycol and admixtures thereof as penetration enhancers for more effective drug absorption though the tympanic membrane.

However, neither Ehrenberger nor Petrus explicitly disclose glycerin or water as the solvent, as recited in claim 11, or a nanoemulsion or liposomal formulation containing a membrane-forming molecule plus a coemulsifier as a permeation accelerator or carrier, as recited in claims 13 and 14.

Mantelle teaches topical compositions of pharmaceutically active agents formulated to produce local effects over a prolonged period of time (col. 5, line 66 to col. 6, line 3). In particular, Mantelle discloses glycerin and water as solvents, as recited in claim 11, as well as dimethylsulfoxide (DMSO) and propylene glycol as solvents which

assist in dermal penetration (col. 7, line 3 to col. 8, line 24), as recited in claims 1-9. The topical compositions of Mantelle can also employ fatty acid emulsifiers capable of forming membranes (lipid bilayers or micelles, i.e., liposomes), such as oleic acid, which is used in combination with lecithin, a well-known phospholipid emulsifying agent (col. 23, Example 36), and can be made as microdispersions (nanoemulsions), as recited in claims 13 and 14.

The compositions taught by Mantelle are for topical administration, and use solvents, carriers, and permeation enhancers identical to those of the claimed formulation. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the compounds of Ehrenberger et al., with the permeation enhancers as taught by Petrus, with the solvents and emulsifiers of Mantelle, because one of ordinary skill would have had a reasonable expectation of success in treating inner ear conditions by directly administering a topical formulation to the tympanic membrane, using a combination of inactive ingredients known in the art to be effective for topical or dermal routes of administration.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 7, and 9 of U.S. Patent No. 5,563,140 in view of Mantelle (US Pat. 5,446,070, issued 8/29/1995) and Petrus (US Pat. 6,093,417, issued 7/25/2000).

Reference claim 9 recites a method of treating neurotoxicity mediated by a glutamate receptor in a mammalian patient having post-synaptic tinnitus,

comprising administering an effective amount of caroverine (1-diethylaminoethyl-3-(p-methoxybenzyl)-1,2-dihydro-quinoxalin-2-one), as recited in examined claims 1, 2, and 4-14. Also, reference claim 3 recites a method of treating neurotoxicity mediated by a glutamate receptor in a mammalian patient, comprising administering an effective amount of hydroxy-caroverine (1-diethylaminoethyl-3-(p-hydroxybenzyl)-1,2-dihydro-quinoxalin-2-one), as recited in examined claim 3. The '140 patent, however, does not recite administration to the inner ear, or in combination with permeation enhancers. 8

As discussed above, Mantelle teaches topical compositions of pharmaceutically active agents formulated to produce local effects over a prolonged period of time (col. 5, line 66 to col. 6, line 3). In particular, Mantelle discloses glycerin and water as solvents, as recited in claim 11, as well as dimethylsulfoxide (DMSO) and propylene glycol as solvents which assist in dermal penetration (col. 7, line 3 to col. 8, line 24), as recited in claims 1-9. The topical compositions of Mantelle can also employ fatty acid emulsifiers capable of forming membranes (lipid bilayers or micelles), such as oleic acid, which is used in combination with lecithin, a well-known phospholipid emulsifying agent (col. 23, Example 36), and can be made as microdispersions (nanoemulsions), as recited in claims 13 and 14.

Petrus teaches topical ear compositions using DMSO and propylene glycol as penetration enhancers for more effective drug absorption though the tympanic membrane (abstract; col. 4, lines 1-15), citing the risks of surgical treatment such as tympanostomy, which can require general anesthesia (col. 2, lines 31-60). Local application of therapeutic agents to the inner ear also places a high dose in direct

proximity to the targeted receptors and avoids disadvantages of oral administration, which disperses the drug systemically and may result in undesirable side effects.

One of ordinary skill in the art, then, would have been motivated to apply the compounds of the '140 patent for treating tinnitus directly to the inner ear, in combination with penetration enhancers to promote tympanic uptake and absorption.

12. Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2, 3, 7, and 10 of U.S. Patent No. 6,573,265, in view of Mantelle (US Pat. 5,446,070, issued 8/29/1995) and Petrus (US Pat. 6,093,417, issued 7/25/2000).

Reference claim 2 recites a method of treating a disease selected from a group including sudden hearing loss, comprising administering an effective amount of caroverine (1-diethylaminoethyl-3-(p-methoxybenzyl)-1,2-dihydro-quinoxalin-2-one), as recited in examined claims 1, 2, and 4-14. Also, reference claim 3 recites the same method, comprising administering an effective amount of hydroxy-caroverine (1-diethylaminoethyl-3-(p-hydroxybenzyl)-1,2-dihydro-quinoxalin-2-one), as recited in examined claim 3. Reference claim 10 recites topical administration of these compounds; however, the '265 patent does not recite administration to the inner ear, or in combination with permeation enhancers.

As discussed above, Mantelle teaches topical compositions of pharmaceutically active agents formulated to produce local effects over a prolonged period of time (col. 5, line 66 to col. 6, line 3). In particular, Mantelle discloses glycerin and water as solvents, as recited in claim 11, as well as dimethylsulfoxide (DMSO) and propylene glycol as

solvents which assist in dermal penetration (col. 7, line 3 to col. 8, line 24), as recited in claims 1-9. The topical compositions of Mantelle can also employ fatty acid emulsifiers capable of forming membranes (lipid bilayers or micelles), such as oleic acid, which is used in combination with lecithin, a well-known phospholipid emulsifying agent (col. 23, Example 36), and can be made as microdispersions (nanoemulsions), as recited in claims 13 and 14.

Petrus teaches topical ear compositions using DMSO and propylene glycol as penetration enhancers for more effective drug absorption though the tympanic membrane (abstract; col. 4, lines 1-15), citing the risks of surgical treatment such as tympanostomy, which can require general anesthesia (col. 2, lines 31-60). Local application of therapeutic agents to the inner ear also places a high dose in direct proximity to the targeted receptors and avoids disadvantages of oral administration, which disperses the drug systemically and may result in undesirable side effects.

One of ordinary skill in the art, then, would have been motivated to apply the compounds of the '265 patent for treating sudden hearing loss directly to the inner ear, in combination with penetration enhancers to promote tympanic uptake and absorption.

Conclusion

13. Claims 1-14 are rejected.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached at. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARA E. CLARK/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612